UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,098	02/05/2007	Adam McCluskey	65617US(54086)	5085

21874 7590 05/29/2008

EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
05/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,098	MCCLUSKEY ET AL.	
	Examiner	Art Unit	
	WALTER E. WEBB	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,26,56-58 and 60-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,26,56-58 and 60-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/2008, 9/11/2007, 5/19/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's elected Group I, claims 1 and 26 for examination on 3/31/2008, which meant that claim 53 and 55-80 were withdrawn from further consideration. However, applicants have subsequently amended claims 56-58 and 60-80 on 5/16/2008 to depend on elected claims 1 or 26. Applicants have also added claims 81-86.

Applicants have elected species "Bis-T23," shown as compound 23 of Table I at pg. 39 of the specification, which reads on claims 1 and 26.

Applicant's election with traverse of is acknowledged. The traversal is on the ground(s) that search of the subject matter of non-elected groups does not constitute a serious burden, especially given the powerful search engines and data bases at the Examiner's disposal. This is not found persuasive because the inventions listed in this action are independent or distinct and require a different field of search. The prior art applicable to one invention would not likely be applicable to another invention.

The requirement is still deemed proper and is therefore made FINAL.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 26, 56-58, and 60-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

"New matter" rejection.

In the instant case, Applicant discloses "contacting dynamin" with an effective amount of a compound of formula I. Applicant states that specific support for this amendment can be found at page 4, lines 6-7. However, this section does not mention "contacting dynamin." It is not dynamin that is being "contacted" but rather cells CONTAINING dynamin. Therefore this phrase constitutes new matter.

Claim 1 contains the amended phrase "dynamin activity" at line 1. Applicant states that specific support for this amendment can be found at page 4, lines 6-7. However, this section does not support the amended phrase. Therefore this phrase constitutes new matter.

Claims 82 and 84 also contain new matter. Claim 82 contains the phrases "diseases or conditions associated with cell vesicle trafficking" and "diseases or conditions characterized by synaptic signal transmission." Claim 84 contains the phrase

"disease or condition is associated with cell vesicle trafficking or is characterized by synaptic signal transmission." Applicant states that support for these phrases can be found at pg. 16, line 28 to page 17, line 2, and pg. 17, line 16-22. However, these sections of the specification do not support these phrases. Therefore, these phrases constitute new matter.

Claim 61 also contain new matter. Claim contains the phrase "side ring." There is no support for "side ring" in the specification in regard to group Z. Therefore, these phrases constitute new matter.

Written Description Rejection

Claims 26 and 86, in particular, claim a "prodrug" of a compound of formula I.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See. E.g., *In re Wilder*, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did 'little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.')

Mere indistinct terms (such as "prodrug" used herein), however, may not suffice to meet the written description requirement. This is particularly true when a compound is claimed in purely functional terms. See *Univ. of Rochester v. G.D. Searle*, 69 USPQ2d 1886 (CAFC 2004) at 1892, stating:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails

to distinguish any steroid form others having the same activity or function. A description of what a material does, rather that of what it is, usually does not suffice. . . . The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

Conversely, a description of a chemical genus will usually comprise a recitation of structural features common to the members of a genus, which features constitute a substantial portion of the genus. See *Univ. of Calf. v. Eli Lilly*, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under section 112, ¶ 1, by showing the enablement of a representative number of species within the genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not specifically define what constitutes a representative number of species, the courts have indicated what des not constitute same. See, e.g., *In re Gostelli*, 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989), holding that the disclosure of two chemical compounds within a subgenus did not adequately describe such subgenus.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include the level of skill and knowledge in the art, partial structure, physical and /or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention form other materials and would lead one f skill in the

art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP 2163.

The present disclosure fails to recite a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation of "prodrug" such that the artisan would readily identify the scope of this active agent. Because there is no support for "prodrug" in the specification, it is not clear that applicant had possession of the claimed invention at the time of filing.

Enablement Rejection

Claims 1, 26, 56-58, and 60-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not reasonably provide enablement for prophylaxis or treatment of disease mediated by dynamin-dependent endocytosis.

1) Prophylaxis of disease

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the breadth of the claims;

3) the predictability or unpredictability of the art;

4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Factors 1 and 2: The claimed invention is drawn to a method of prophylaxis or therapeutic treatment of disease or condition in a mammal mediated by dynamin-dependent endocytosis. Here, prophylaxis is tantamount to a cure or prevention of disease.

Factors 3 and 7: In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the prevention or cure of disease or condition in a mammal mediated by dynamin-dependent endocytosis, could be effectively achieved by the administration of the claimed active agent.

Treatment of epilepsy, for example, is well developed (see Duncan et al., The Lancet 2006), but the state of the art with regard to preventing epilepsy is grossly underdeveloped.

In this regard, Duncan et al. is cited. Duncan et al. discloses that drug treatment of epilepsy is effective in only 60-70% of individuals and that the aim of the treatment is to control the size of the seizures as quickly as possible. (See Drug Treatment at pg. 1092.) They also teach that for some a cure is possible through a neurosurgical procedure. (See abstract.) Therefore, treating this disease is unpredictable, and as such the artisan would not accept that disease or condition in a mammal mediated by dynamin-dependent endocytosis in general can be prevented with applicant's claimed compound. In particular, there is no known agent that is effective against preventing epilepsy.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, there is no apparent disclosure to support the contention that the prevention of disease or condition in a mammal mediated by dynamin-dependent endocytosis in general can be achieved as claimed by applicant.

Factor 4: Applicant did not disclose, for example, a protocol or guidance as to how prevention or cure of disease or condition in a mammal mediated by dynamin-dependent endocytosis. Applicant merely shows a relationship between endocytosis and some human diseases. Applicant's disclosure is inadequate as to directing or

guiding how the proposed agents can be employed to accomplish such objectives in a predictable manner.

Factor 5: The specification provides no examples of treatment or prevention of any disease with the claimed active agent. Applicant does show experimental data involving GTPase binding assays, and endocytosis. While the present claims encompass preventing disease or condition in a mammal mediated by dynamin-dependent endocytosis, Applicant's data merely shows support for treatment through *in vitro* experimentation.

Factor 6: The burden of preventing disease or condition in a mammal mediated by dynamin-dependent endocytosis with the claimed compound is much greater than that of treating a specific disease, with a specific compound. Since the present specification would not enable the skilled artisan to prevent disease or condition in a mammal mediated by dynamin-dependent endocytosis with the claimed compound, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice the full scope of the presently claimed invention.

Factor 8: In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

3)Scope of the diseases being treated

Given the unpredictable nature of treating epilepsy cited in the art above, one of ordinary skill in the art would not accept on its face that applicant's claimed active agent could treat diseases or conditions in a mammal mediated by dynamin-dependent endocytosis in general. Dynamin is part of a family of GTP-binding proteins with multiple functions affecting many processes throughout the body. There is no support in applicants disclosure for the breadth of diseases related in any way to dynamin-dependent endycytosis. The artisan would be subject to undue experimentation in determining which diseases are related to dynamin-dependent endocytosis as well as determining which of the diseases found showed some sensitivity to a compound of formula I. Applicants disclosure is not commensurate in scope with applicant's claims.

4)Scope of active agents

The specification does not adequately enable a person having ordinary skill in the art to use the claimed invention in light of the scope of compounds formula I, which, as claimed, have a plethora of functional groups including a vast range of heteros. There is no reasonable basis for assuming that myriads of compounds not made and thus not tested will share the requisite minimum activity needed to practice the invention, especially when receptor binding is generally known to be structure sensitive. See In re Fisher, 166 USPQ 18, and In re Surrey, 151 USPQ 724 in regards to sufficiency of disclosure in cases directed to structure sensitive arts. The Examiner acknowledges that the applicant is not required to test every compound, but further guidance is need in order for the artisan to practice the invention without undue

experimentation. Applicant's disclosure is inadequate as to directing or guiding how dimeric tyrophostin can be employed to predictably inhibit dynamin activities other than GTPase activity or how other compounds represented by formula I can predictably inhibit the GTPase activity and other activities of dynamin. For example, it is known in the art that dynamins play a role in cell growth, cell spreading, and neurite outgrowth. (See Urrutia et al., Proc. Natl. Acad. Sci. 1997, at abstract and Multiple Functions for the Dynamin Family at pp. 382-383.)

Summary

As the discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the artisan with a reasonable expectation that preventing or treating disease or condition in a mammal mediated by dynamin-dependent endocytosis in general with the claimed compound could be achieved. In order to actually achieve such an objective, it is clear from the discussion above that the artisan could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. The artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 1, 26, 56-58, and 60-86 are deemed properly rejected.

Indefiniteness Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26, 56-58, 60-78 and 80-85 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 contains the phrase “condition in a mammal mediated by dynamin-dependent endocytosis.” This phrase is indefinite since the term “mediated” is a “term of degree” which is inadequately defined. Specifically, the specification provides insufficient guidance for determining what degree of correlation between dynamin-depedent endocytosis and a particular condition required for it to be "mediated" thereby, as compared to a disease state in which dynamin-dependent endocytosis is merely present and causes ancillary symptoms, but is not is implicated in the core etiology of the disease.

Claim 61 contains the phrase “side ring.” This phase is indefinite since its modifying function is unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 79 and 86 are rejected under 35 U.S.C. 102(b) as being anticipated by Gazit et al., (Journal of Medicinal Chemistry 1996).

Gazit et al. teach the elected species of formula I, Bis-T23. See Table 1 structure number 5 at page 4907. They teach that this compound and compounds like it, known as tyrphostins, are potent inhibitor of EGF receptor tyrosine kinase. (See abstract.) They also teach that these compounds can selectively inhibit different PTK's, such as Src family kinases.[1] They teach that their dimeric inhibitors are expected to have enhanced efficacy as compared to the monomeric inhibitors. (See Introduction, 4th paragraph.)

The reference is anticipatory insofar as claim 1 recites a biochemical mechanism in only the broadest terms. When Bis-T23 is administered, it will inherently inhibit dynamin "activity." Here, any amount of inhibition whatsoever would be sufficient to find anticipation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

[1] Here the reference directs the reader's attention to references 4-6. Reference 4 has been provided for support.

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 79 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gazit et al., (Journal of Medicinal Chemistry 1996) in view of Ahn et al., (Journal of Biological Chemistry 1999.) This presumption is made here purely *arguendo*, in the interest of completeness of prosecution, since as stated above the examiner believes the reference to be anticipatory.

Gazit et al. teach the elected species of formula I, Bis-T23. See Table 1 structure number 5 at page 4907. They teach that this compound and compounds like it, known as tyrphostins, are potent inhibitor of EGF receptor tyrosine kinase. (See abstract.) They also teach that these compounds can selectively inhibit different PTK's, such as Src family kinases.[2] They teach that their dimeric inhibitors are expected to have enhanced efficacy as compared to the monomeric inhibitors. (See Introduction, 4th paragraph.)

Gazit et al. differs from the instant claims insofar as it does not teach inhibiting dynamin activity.

[2] Here the reference directs the reader's attention to references 4-6. Reference 4 has been provided for support.

Ahn et al. teach that Src-mediated tyrosine phosphorylation of dynamin is essential for its function in clathrin mediated G protein-coupled receptor endocytosis. (See abstract.)

It would have been obvious to a person having ordinary skill in the art at the time of applicant's invention to inhibit dynamin activity with the compound of Gazit, since the compound inhibits Src tyrosine kinase and Src tyrosine kinase phosphorylates dynamin, which is essential for dynamin endocytosis activity. Ahn shows in figure 1 at page 1186 that inhibition of the Src tyrosine kinase inhibits the activity of dynamin. Because the compounds of Gazit also inhibit Src tyrosine kinase, they would also inhibit the activity of dynamin.

Claims 26, 56-58, 60-78 and 80-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gazit et al., (Journal of Medicinal Chemistry 1996) in view of Jassar et al., (Brain Research 1997).

Gazit et al., taught above, differs from the instant claims 26, 56-58, 60-78 and 80-85 insofar as it does not teach a therapeutic treatment of a disease or condition mediated by dynamin-dependent endocytosis, where the disease is epilepsy.

Jassar teach that phosphorylation is important for the activation and long term maintenance of $GABA_A$ receptor function and that protein tyrosine kinase (PTK) modulates GABA mediated neurotransmission in the forebrain. (See abstract) They also teach that tyrphostin B-44 (-) attenuates $GABA_A$ receptor responses. (See section 3.2 Inhibition of PTK attenuates $GABA_A$ receptor responses at pg. 129.) They teach

that understanding these mechanisms of GABA may have important therapeutic implications in conditions such as epilepsy where GABA neurotransmission is aberrant. (See Discussion, last paragraph at pg. 133.)

It would have been obvious to a person having ordinary skill in the art to use the compound of Gazit in a method for treating epilepsy, since GABA neurotransmission is aberrant in epilepsy and GABA neurtransmission can be attenuated by inhibition of PTK. The artisan would be motivated to use a compound of Gazit, since Gazit teaches that their dimeric tryphostin has enhanced efficacy of monomeric tyrphostin, such as the one used in Jassar. The artisan would therefore expect better attenuation of GABA receptor responses with the compound of Gazit.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 8:00am-4:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb
/Walter E Webb/
Examiner, Art Unit 1612

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612